DTU Library

Effects of the relative timing of opposite-polarity pulses on loudness for cochlear implant listeners

Guérit, François; Marozeau, Jeremy; Deeks, John M.; Epp, Bastian; Carlyon, Robert P.

Published in:
Journal of the Acoustical Society of America

Link to article, DOI:
10.1121/1.5070150

Publication date:
2018

Document Version
Publisher's PDF, also known as Version of record

Effects of the relative timing of opposite-polarity pulses on loudness for cochlear implant listeners

François Guérit,[1,a)] Jeremy Marozeau,[1] John M. Deeks,[2] Bastian Epp,[1] and Robert P. Carlyon[2]

[1]*Hearing Systems Group, Department of Electrical Engineering, Technical University of Denmark, 352 Ørsteds Plads, Kongens Lyngby, 2800, Denmark*

[2]*Medical Research Council Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge, CB2 7EF, United Kingdom*

(Received 21 February 2018; revised 15 October 2018; accepted 19 October 2018; published online 9 November 2018)

The symmetric biphasic pulses used in contemporary cochlear implants (CIs) consist of both cathodic and anodic currents, which may stimulate different sites on spiral ganglion neurons and, potentially, interact with each other. The effect on the order of anodic and cathodic stimulation on loudness at short inter-pulse intervals (IPIs; 0–800 μs) is investigated. Pairs of opposite-polarity pseudomonophasic (PS) pulses were used and the amplitude of each pulse was manipulated independently. In experiment 1 the two PS pulses differed in their current level in order to elicit the same loudness when presented separately. Six users of the Advanced Bionics CI (Valencia, CA) loudness-ranked trains of the pulse pairs using a midpoint-comparison procedure. Stimuli with anodic-leading polarity were louder than those with cathodic-leading polarity for IPIs shorter than 400 μs. This effect was small—about 0.3 dB—but consistent across listeners. When the same procedure was repeated with both PS pulses having the same current level (experiment 2), anodic-leading stimuli were still louder than cathodic-leading stimuli at very short intervals. However, when using symmetric biphasic pulses (experiment 3) the effect disappeared at short intervals and reversed at long intervals. Possible peripheral sources of such polarity interactions are discussed.

https://doi.org/10.1121/1.5070150

[ICB] Pages: 2751–2763

I. INTRODUCTION

In normal-hearing listeners, action potentials (APs) in response to sounds are generated at the very peripheral end of the spiral ganglion neurons (SGNs) that constitute the auditory nerve (AN; Kim and Rutherford, 2016). For cochlear implant (CI) users, however, electrical current can theoretically elicit APs at both the peripheral and central axons of the SGNs (van den Honert and Stypulkowski, 1984; Javel and Shepherd, 2000). As a result, a given electrical pulse could produce APs that differ in the latency after which they arrive at the cochlear nucleus, with APs generated at the peripheral processes arriving later than those generated at the central axons. Perhaps more importantly, there is evidence that stimulation of the different sites could interact, for example, by an AP generated at the peripheral process being blocked by the effect of the stimulus on the central axon (Frijns *et al.*, 1996; Rattay *et al.*, 2001). Here we briefly review evidence that the site of activation depends on the polarity of electrical stimulation, and describe ways in which APs generated at different sites may interact to affect perception. We then describe a series of experiments that investigate these possible interactions by using pairs of opposite-polarity pulses. We show that the loudness of these pulse pairs depends systematically both on their order and the inter-pulse-interval (IPI) between them, and discuss the results in terms of possible underlying biophysical and physiological mechanisms.

A. Latency distribution in animal recordings

One method to determine whether APs have been generated at the peripheral or central process of the SGNs is to compare the latency of APs elicited by electric pulses of different intensity and polarity (van den Honert and Stypulkowski, 1984; Javel and Shepherd, 2000; Miller *et al.*, 1999; Undurraga *et al.*, 2013). Javel and Shepherd (2000) measured single-neuron spike latencies at the level of the inferior colliculus (IC) in cats, and observed a multimodal distribution of latencies in response to biphasic electrical pulses. They attributed these multiple latencies to different generation sites, including the cochlear hair cells and the peripheral and central processes of the AN. They estimated the latency difference between spikes elicited at peripheral and central AN processes to be in the range of 100–200 μs.

Spike latencies can also be affected by the polarity of the electrical stimulus. Miller *et al.* (1999) measured cat single-neuron responses at the level of the nerve trunk when stimulated with cathodic or anodic monophasic pulses

a)Current address: MRC Cognition and Brain Sciences Unit, University of Cambridge, 15 Chaucer Road, Cambridge CB2 7EF, United Kingdom. Electronic mail: francois.guerit@mrc-cbu.cam.ac.uk

presented in monopolar mode (i.e., with the ground outside the cochlea). Responses to cathodic currents exhibited longer latencies and lower thresholds than for anodic currents, suggesting that cathodic currents evoke APs more peripherally than anodic currents. This is consistent with modeling work of Rattay *et al.* (2001), based on observations from Ranck (1975), which suggests that a locally positive second derivative of the voltage along the axons of the SGNs can trigger APs. The location of those areas of positive second derivative changes with polarity, being near the electrode with cathodic currents and farther away for anodic currents (Ranck, 1975).

The aforementioned studies suggest that anodic currents activate the neurons more centrally than cathodic currents. If this is true, by using anodic vs cathodic currents, one could target central and peripheral processes, respectively. It could also be that both polarities excite nodes of Ranvier on the same side (either peripheral or central) of the soma. Miller *et al.* (1999) hypothesized that most of the neurons they studied had been excited for both polarities along the central axons. Cartee *et al.* (2006) suggested a greater peripheral activation, at least with cathodic currents.

The studies from Miller *et al.* (1999) and Cartee *et al.* (2006) were performed in acutely deafened animals, where the peripheral processes of the SGNs were likely to be intact or have a low degree of degeneration. This is not the case for human CI listeners, where years of auditory deprivation lead to the progressive degeneration of the SGNs, starting with the peripheral processes (Johnsson *et al.*, 1981; Leake and Hradek, 1988). The observation by Miller *et al.* that cathodic currents elicited lower thresholds than anodic currents might therefore not hold if peripheral processes are degenerated.

B. Polarity studies in human CI listeners

Monophasic pulses cannot be used in humans because the charge imbalance would cause electro-chemical damage to the tissues in the cochlea (Brummer and Turner, 1977). However, the effect of stimulus polarity has been studied using triphasic, quadraphasic, or asymmetric biphasic pulses (Bahmer *et al.*, 2010; Bahmer and Baumann, 2013, 2016; Bahmer *et al.*, 2017; Carlyon *et al.*, 2013; Macherey *et al.*, 2006; Macherey *et al.*, 2008; Macherey *et al.*, 2010; Macherey *et al.*, 2017; Undurraga *et al.*, 2013; Karg *et al.*, 2013, van Wieringen *et al.*, 2005). Psychophysical experiments using those pulses have shown that anodic currents are more efficient (i.e., require less current) than cathodic currents in eliciting a response at comfortable levels (Macherey *et al.*, 2008). The difference between the two polarities is greatest at higher levels (Undurraga *et al.*, 2013) and is consistent across devices and listeners (Carlyon *et al.*, 2013). At threshold, numerous studies have failed to show consistent effects of polarity (anodic vs cathodic or anodic-first vs cathodic-first single pulses: Bahmer and Baumann 2013; Hughes *et al.*, 2017; Karg *et al.*, 2013; Macherey *et al.*, 2006; Macherey *et al.*, 2017; Mesnildrey, 2017; Undurraga *et al.*, 2013). However, although the direction and size of the polarity effect differs across listeners and electrodes, these differences can be both reliable and substantial for individual subject-electrode combinations (Carlyon *et al.*, 2018; Macherey *et al.*, 2017). There is also electrophysiological evidence, using supra-threshold stimuli, that anodic stimulation is both more efficient than cathodic stimulation and it excites a more central site on the SGN. Undurraga *et al.* (2013) reported that wave V of the electrically evoked auditory brainstem response (eABR) to anodic stimulation was larger than for cathodic stimulation, and also had a shorter latency (difference of 153 μs in average). This is consistent with cathodic stimulation eliciting APs at a more peripheral site, hence, with a longer traveling time toward the brainstem.

C. Perceptual effects of stimulation at different sites

Because APs elicited at peripheral and central sites are likely to interact and arrive at the brain with different latencies, they potentially disrupt the information coded in the timing of the neural response. Perhaps more importantly, the polarization of a central site on a neuron may affect the propagation of spikes elicited at a peripheral site, and this could increase the current needed for the stimulus to be heard and/or reach a comfortable loudness (Macherey *et al.*, 2017).

The present study examined the interactions between the effects of anodic and cathodic stimulation at short IPIs (0–800 μs) on loudness. For many stimuli such as the symmetric biphasic pulses used clinically, the anodic phase is likely to dominate the loudness. Therefore, experiments 1a and 1b used a paradigm with pairs of equally loud opposite-polarity pseudomonophasic (PS) pulses (Fig. 1). We measured the change in perceived loudness when varying both the order of those pulses and the duration of the silent interval between them. Experiments 2 and 3 studied the same interactions with stimuli where the current levels, rather than the loudness, of cathodic and anodic stimulation were equal (see Fig. 1). We hypothesized that a difference in site of AP generation with polarity would create order effects for the perceived loudness of anodic and cathodic currents presented sequentially. For example, activation of central and peripheral sites is more likely to interact when the peripheral stimulation occurs first than when the central stimulation occurs first. In the latter case, APs can propagate centrally, unimpeded by the subsequent stimulation of the peripheral processes. Any such order effects should be largest at IPIs below 200 μs, the estimated latency difference between peripheral and central stimulation (Miller *et al.*, 1999).

II. EXPERIMENTS 1a AND 1b: EQUALLY LOUD ASYMMETRIC PULSES

A. Methods

1. Listeners

Five post-lingually deaf recipients of an Advanced Bionics CI (Valencia, CA; including one bilateral CI user) participated, amounting to six ears being tested. Their details are shown in Table I. Listeners were recruited both in Cambridge (UK) and Copenhagen (DK), and the experimental procedure was approved by the National Research Ethics Committee for the East of England (Ref. No. 00/327) and the Danish Science-Ethics Committee (Ref. No. H-

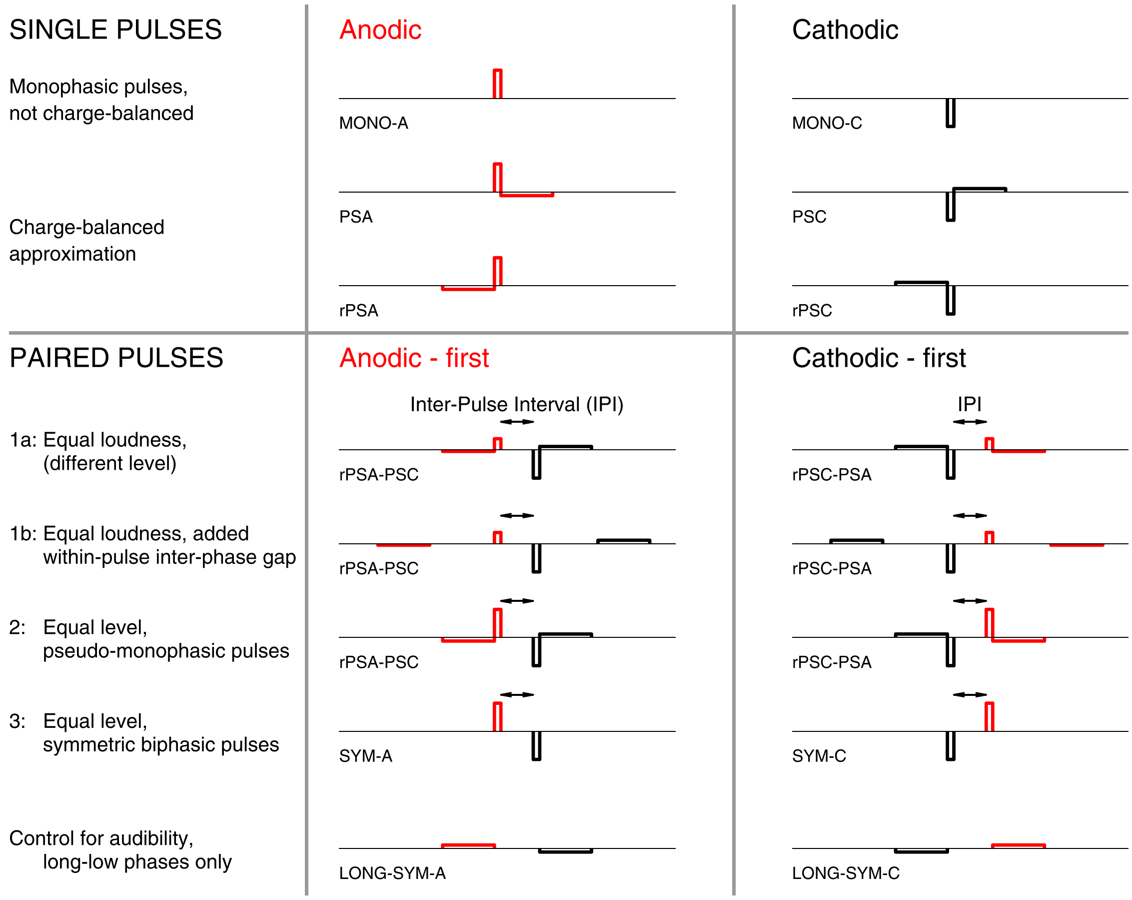

FIG. 1. (Color online) (Top) Pulse shapes commonly used for polarity studies (e.g., for humans, pseudomonophasic anodic and cathodic, respectively, PSA and PSC). Reverted version of PSA and PSC are labeled with a "r" (rPSA and rPSC). (Bottom) Pulse-pair stimuli used for the different experiments of this study. By using pairs of pseudomonophasic (PS) pulses, we could mimic biphasic pulses having different levels for each phase, while staying charge-balanced.

16036391), respectively. All listeners signed a participation agreement before data collection began.

2. Setup and safety

All data collection was achieved by means of direct stimulation, using Advanced Bionics research hardware (CPI-2 clinical interface, PSP speech processor; Valencia, CA) and software (BEDCS 1.18, Valencia, CA). Current levels were limited by ensuring that the voltage at the electrode stayed below limits of compliance (7 V in the HiRes90k Advanced Bionics implant) and that charge density stayed below 100 μC/cm^2 (Litovsky *et al.*, 2017). Stimuli were checked using a test implant and digital storage oscilloscope. Impedance checks were performed at the beginning and end of each testing session.

3. Stimuli

The stimuli consisted of PS pulses, with a 43-μs short-high phase preceded (reversed pseudomonophasic anodic and cathodic, rPSA and rPSC) or followed [pseudomonophasic anodic (PSA) and pseudomonophasic cathodic (PSC)] by a 344-μs 1/8 amplitude phase of opposite polarity (Fig. 1). With such asymmetric pulses, most neural excitation comes from the short-high phase (Miller *et al.*, 2001b; Undurraga *et al.*, 2013). We therefore refer to the asymmetric pulses with the short-high phase being anodic or cathodic as the "anodic" and "cathodic" pulse, respectively.

TABLE I. Demographics of the CI listeners. All listeners were post-lingually deaf recipients of an Advanced Bionics HiRes90k device (Valencia, CA) with two different types of electrode arrays. "1j" is a straight array and "Helix" is a curved, perimodiolar array. S1 was recruited in Denmark, all the other listeners (with identification, ID, starting with AB) were recruited in the United Kingdom.

Listener identification	Age (yr)	Duration of implant use (yr)	CI Side	Electrode used for testing	Electrode array	Etiology
S1-L	60	9	Left	9	1j	Pendred syndrome
S1-R		10	Right	9	Helix	
AB1	72	8	Left	9	1j	Unknown
AB2	57	9	Left	9	1j	Ototoxicity
AB3	71	10	Left	9	1j	Otosclerosis
AB5	75	7	Left	10	1j	Otosclerosis

A pulse-pair paradigm (rPSA-PSC and rPSC-PSA, Fig. 1, row 1a) allowed us to adjust the relative level of each pulse so that both polarities elicited an equal loudness when presented separately. These anodic- and cathodic-first pulse pairs were created with eight different inter-pulse intervals (IPIs) of 0, 50, 100, 200, 400, and 800 μs. One subject, AB1, was additionally tested at an IPI of 1600 μs. For all experiments, a single electrode in the middle of the array was used (number 9 or 10, typically assigned to frequencies of about 1600 Hz by the clinical speech processor, corresponding to frequencies of about 3000 Hz in an acoustically stimulated cochlea; Landsberger *et al.*, 2015). Each pulse pair was presented at a 100-Hz repetition rate for a duration of 400 ms. Note that throughout this article we use the abbreviation IPI to refer to the zero-amplitude interval *between* pulses, and refer to the gap between the two phases of a single pulse as the inter-phase or within-pulse gap.

4. Loudness matching of the single pulses

In this procedure, the current level of a comparison train of single pulses (either rPSC, PSA, or rPSA pulse trains, Fig. 1) was adjusted to have the same loudness as the reference stimulus, which was a train of single PSC pulses. The current level of the reference pulse train was determined using a set of preliminary measures to ensure that, when eventually combined into trains of pulse pairs, no stimulus would be uncomfortably loud. Those preliminary measures consisted of measuring the most comfortable levels (MCLs) of trains of pulse pairs in all possible combinations (two orders and six IPIs) used in the main experiment, but with the pulses in each pair having the same current level. The current level corresponding to the lowest MCL was then used as the level of the PSC pulse train used in the loudness balancing procedure described below. MCLs were obtained using an 11-point chart on which point 6 corresponded to MCL (labeled "most comfortable").

In each run of the loudness balancing procedure, the experimenter presented the PSC pulse train and one other pulse train sequentially, and, after each presentation, asked the listener which was louder. One of these two stimuli was designated the reference and the other the comparison, and the current level of the comparison was adjusted to have the same loudness as the reference by bracketing several times around it. The final value was computed from the mean difference (in dB) of two runs, with the PSC pulse train being the reference in one run and the comparison stimulus in the other. The resulting equally loud pulses were then combined into the pulse-pair (rPSA-PSC and rPSC-PSA) stimuli shown in the row labeled 1a in Fig. 1. Finally, we checked that none of these levels caused loudness to exceed the MCL for any of the IPIs by using a loudness scaling chart and progressively increasing the current levels.

5. Loudness ranking

Anodic- and cathodic-first pulse-pair stimuli at all IPIs were loudness ranked using the optimally efficient mid-point comparison algorithm (Long *et al.*, 2005). The procedure consists of a succession of two-interval forced-choice presentations, without feedback, where the listeners indicate which stimulus is the loudest. The ranks of the stimuli are updated as more comparisons are made. Each new stimulus is first compared with the one in the middle of the provisional ranking and then to the middle of either the top or bottom half of the ranks, depending on the response. Subsequent comparisons are made until a unique position for that stimulus is identified. This procedure was repeated 12 times, in 2 blocks of 6 repetitions. A single PSC pulse was included in the loudness-ranking procedure for listeners AB3, S1-L, S1-R, and AB5. This PSC pulse had the same current level as in the rPSA-PSC pulse-pair stimulus. Inclusion of the single PSC pulse allowed us to test whether both pulses contributed to the overall loudness. If the pulse-pair stimuli were louder than their component single pulses, we could conclude that both pulses contributed to loudness. If the pulse-pair stimuli were not louder, the results would be inconclusive: either one pulse dominated loudness, or both pulses contributed but partially counteracted each other, for example, by charge cancellation.

6. Loudness matching of trains of pulse pairs

Loudness ranking only gives a qualitative indication (which stimuli are louder than others), but does not quantify how much this difference is in terms of decibels. To obtain this information, we matched the loudness of the opposite-polarity pulse-pair stimuli at IPIs of 50 and 200 μs. The difference (in dB) needed to equate loudness was computed from the average of four runs (two runs with anodic-first as the reference, two runs with cathodic-first), where the experimenter bracketed the level around the point of subjective equality. The level difference (in dB) between anodic and cathodic pulses comprising each pulse pair was kept constant throughout the procedure.

7. Effect of adding a within-pulse inter-phase gap

Even though we assume that most of the neural excitation comes from the short-high phases in our stimuli, the long-low phases could theoretically influence the results as well, for example, by interacting with the short-high phases. To control for this, experiment 1b repeated the loudness-balancing procedures from experiment 1a with five of the listeners and added a within-pulse 600-μs gap between the long-low and the short-high phase of each pulse (cf. Fig. 1).

B. Results

1. Loudness matching of the single pulses

Figure 2(A) shows the results of matching the loudness of rPSA, PSA, and rPSC pulse trains to a PSC pulse train in experiment 1a. The most obvious feature of the results is the well-established finding that, to achieve the same loudness, much (2.1 dB) less current is needed for anodic pulses than for cathodic pulses. In addition, the "reversed" PS pulses (in which the long-low phase occurs before the short-high phase) require slightly (0.1 dB) more current than their non-reversed counterparts. These findings were confirmed by a two-way (polarity vs "reversing" of pulses) repeated-measures analysis of variance (ANOVA) on the levels in dB re 1 uA [polarity: $F(1,5) = 49.9$, $p < 0.001$, reversing: $F(1,5) = 10.81$, $p = 0.022$, interaction: $F(1,5) = 1.58$, $p = 0.265$]. Note that, because of the small number of ears tested we repeated all statistical analyses described in this article using a mixed-effects linear model approach (Kuznetsova *et al.*, 2015; Kuznetsova *et al.*, 2017) so as to check the robustness of the findings to the assumptions made about the underlying distribution of the data. Those analyses, described in more detail in Sec. IV, led to the same conclusions as obtained using the repeated measures ANOVA (rmANOVAs) described here and in Sec. III B.

Figure 2(B) shows the results of matching the loudness of the single pulses when adding an extra 600-μs within-pulse gap between the long-low and short-high phases (experiment 1b). For the listeners who performed both experiments the effects of polarity and ordering were 2.1 dB and −0.1 dB, respectively, roughly similar to the 1.9 dB and 0.1 dB in experiment 1a [rmANOVA on the matched levels, polarity: $F(1,4) = 33.0$, $p < 0.001$, reversing: $F(1,4) = 3.22$, $p = 0.147$, interaction: $F(1,4) = 18.4$, $p = 0.013$]. To evaluate the effect of the 600-μs within-pulse gap of experiment 1b on the pattern of results, we performed a rmANOVA on the single-pulse levels from experiments 1a and 1b with the effects of experiment, polarity, and reversing as factors. The results, shown in Table II, reveal no interaction between the effects of experiment and polarity, but there was an interaction between experiment, polarity, and reversing [$F(1,4) = 13.5$, $p = 0.02$]. These interactions reflect the fact that, to reach the same loudness, PSA pulse trains needed more current than rPSA pulse trains in experiment 1b but not in experiment 1a. Not surprisingly, the effect of polarity, which was highly significant for each experiment alone, remained significant in the combined analysis.

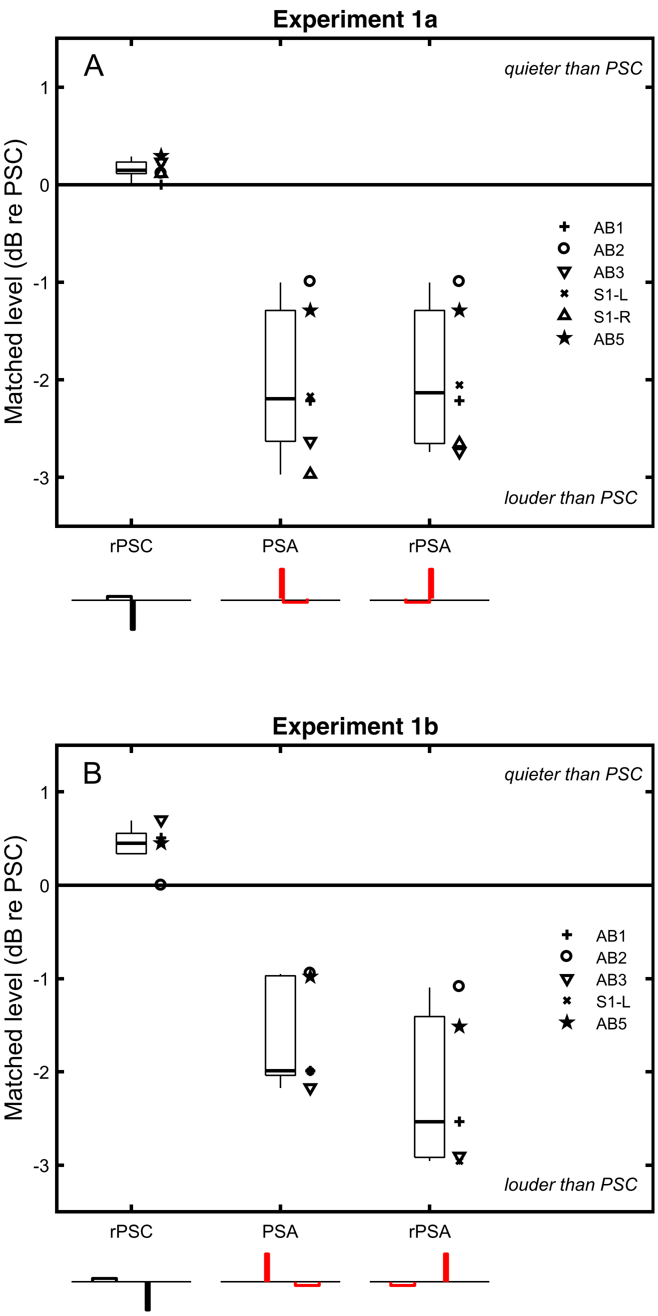

FIG. 2. (Color online) (A) Levels of the single pulses used in experiment 1a, relative to the PSC pulse. Anodic pulses required on average 2.1 dB less current to elicit the same loudness than cathodic pulses. (B) Levels used in experiment 1b. Subject S1-R did not participate in that experiment.

2. Loudness ranking and matching of pulse-pair stimuli, experiment 1a

Mean loudness ranks[1] and standard errors across trials for all listeners of experiment 1a are shown in Fig. 3. As not all listeners had the same number of conditions in this experiment, ranks were scaled between 1 and 10 for comparison across listeners. This was done using the formula $x = 9[(y - 1)/(N - 1)] + 1$, where x is the transformed rank, y is the original rank, and N is the number of ranked stimuli. Note that, although the anodic- and cathodic-first data are plotted in separate panels, all stimuli were loudness-ranked together as part of the same procedure.

Figure 3 shows that loudness ranks for the pulse pairs increased with increasing IPI and were greater for anodic-first than for cathodic-first pulse pairs. Furthermore, the polarity effect was greatest at shorter IPIs. These findings were supported by a rmANOVA on the mean ranks (excluding the single PSC stimulus), which showed significant effects of polarity [$F(1,5) = 131.1$, $p < 0.001$] and of IPI [$F(5,25) = 113.8$, $p < 0.001$], and a significant interaction between IPI and polarity [$F(5,25) = 34.72$, $p < 0.001$]. Interestingly, all pulse pairs with an IPI of 50 μs or longer were louder than the single PSC pulse, indicating that both pulses in each pair must contribute to loudness. At 0 μs, the pulse-pair stimuli had a similar loudness to the single PSC pulse. The effect of polarity is further

TABLE II. Results of the repeated-measures ANOVA on the single pulse levels from experiments 1a and 1b (data shown in Fig. 2). p values below 0.05 are highlighted in bold.

Effect	F ratio $F(1,4) =$	p value
Experiment	3.23	0.147
Polarity	36.2	**0.00384**
Reversing	0.00702	0.937
Experiment × polarity	3.29	0.144
Experiment × reversing	6.09	0.0690
Polarity × reversing	20.8	**0.0103**
Experiment × polarity × reversing	13.5	**0.0213**

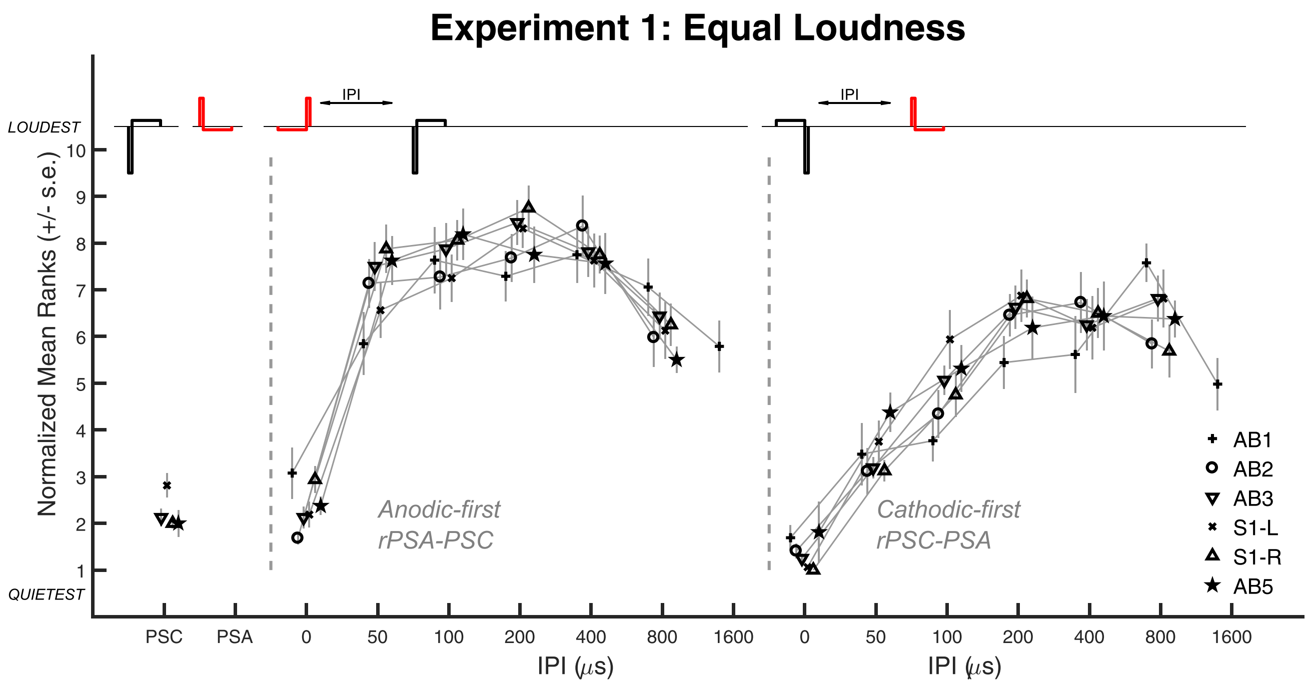

FIG. 3. (Color online) Results of the loudness ranking procedure for experiment 1 (equal loudness between anodic and cathodic stimulation). Ranks for each subject were scaled between 1 and 10. Single PSA was not included in this experiment, as it was loudness matched to PSC.

illustrated by the dark grey bars of Fig. 4(A), which plots the difference in ranks between the two polarities at each IPI. It can be seen that, for IPIs up to 400 μs, the anodic-first pulses were ranked louder than cathodic-first pulses. This difference was largest at IPIs of 50 and 100 μs, hence the interaction between the effects of polarity and IPI.

Subsequent loudness matching [Fig. 4(B), dark grey bars] between the anodic- and cathodic-first pulse pairs at IPIs of 50 and 200 μs confirmed that the anodic-first stimuli were louder than cathodic-first stimuli [effect of polarity on the matched levels, $F(1,4) = 101.8$, $p < 0.001$]. The difference was numerically larger when the IPI was 50 μs than when it was 200 μs (0.38 dB vs 0.17 dB, respectively), but did not differ significantly between the two IPIs [interaction between IPI and polarity, $F(1,4) = 3.01$, $p = 0.16$].

3. Loudness matching of pulse-pair stimuli, experiment 1b

In experiment 1b, we added an extra within-pulse inter-phase gap of 600 μs between the long-low and short-high phases (Fig. 1, experiment 1b), and performed loudness matching at IPIs of 50 and 200 μs. This was done so as to study whether the order effects observed in experiment 1a were likely due to interactions between the long-low and short-high phases—the rationale being that any such interactions would be reduced by increasing the within-pulse inter-phase gaps. Results are shown in Fig. 4(B) (white bars). Similar to experiment 1a, less current was needed for anodic-first than for cathodic-first stimuli to obtain the same loudness [polarity effect averaged across IPIs, $t(4) = 9.25$, $p < 0.001$]. A rmANOVA, including experiments 1a and 1b, showed a significant effect of IPI [$F(1,4) = 12.8$, $p = 0.023$] and experiment [$F(1,4) = 16.4$, $p = 0.015$] on the level differences between anodic- and cathodic-first pulses, but no interaction between experiment and IPI [$F(1,4) = 3.4$, $p = 0.15$]. The main effect of experiment reflects the fact that overall, the difference between opposite-polarity stimuli was larger in experiment 1b than in experiment 1a [$t(4) = 4.05$, $p = 0.016$]. The main effect of IPI reflects the fact that the difference between anodic-first stimuli and cathodic-first stimuli (i.e., anodic-first stimuli being louder than cathodic-first stimuli) was larger at the 50- than at the 200-μs IPI [$t(4) = 3.57$, $p = 0.023$].

III. EXPERIMENTS 2 AND 3: EQUAL-LEVEL AND SYMMETRIC- BIPHASIC PULSE PAIRS

As the loudness was matched between anodic and cathodic asymmetric pulses in experiment 1, the cathodic pulses in each pair had, on average, a current level that was 2.1 dB higher than that of the anodic pulses. It is possible that the effects observed in experiment 1 were driven by the relative current levels rather than by the polarities of the first and second pulses. Therefore, experiment 2 presented both pulses at the same level. We would then expect most of the excitation to arise from the anodic pulse.

Experiment 3 used symmetric biphasic pulses (SYM-A and SYM-C, Fig. 1). SYM-A and SYM-C were effectively the same stimuli as in experiment 2, but without the flanking long-low phases and with a slightly lower level due to any effect of the long-low phases on the MCLs in experiment 2. Thus, by comparing experiments 2 and 3, we aimed to characterise the influence of those long-low phases on the effects of varying the IPI and polarity. In the particular case of experiment 3, changing the IPI is equivalent to changing the inter-phase (within-pulse) gap of a symmetric biphasic pulse. When this gap was zero, the individual pulses resemble those used clinically in many devices.

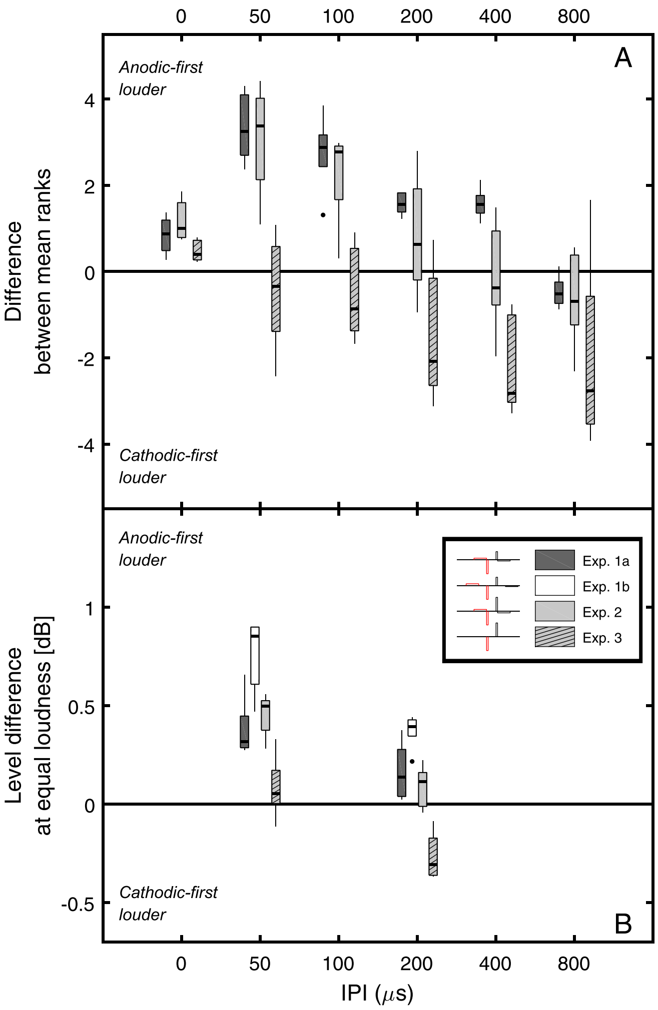

FIG. 4. (Color online) (A) Difference between the mean ranks obtained with anodic-first vs cathodic-first stimuli. The boxes show the distribution of individual results ($N = 5$, subject S1-R not shown in experiment 1a), with positive values indicating a higher rank given to anodic-first stimuli. Experiment 1a: equal loudness between cathodic and anodic pulses in isolation. Experiment 2: equal level. Experiment 3: symmetric biphasic pulses. (B) Results of the loudness matching between anodic- and cathodic-first stimuli at 50- and 200-μs IPI. Positive values indicate that anodic-first stimulus is louder than cathodic-first. Experiment 1b: equal loudness between cathodic and anodic pulses in isolation, with a 600-μs gap between the long-low and short-high phases of the PS pulses. Lower and upper limits of the boxes: 25th and 75th percentiles of the ranks. Horizontal black line (and blue line): median rank. Whiskers: 25th (or 75th) percentile minus (or plus) 1.5 the interquartile range. Dots correspond to data points with values outside the range delimited by the whiskers.

A. Methods

1. Listeners

The same five listeners as in experiment 1b participated in experiments 2 and 3. Listener S1 only participated with her left ear (S1-L), since her right implant had a failure. Hence, five ears were tested.

2. Loudness ranking and matching

Trains of anodic- and cathodic-first pulse pairs with IPIs ranging from 0 to 800 μs, as well as trains of single PSC pulses were loudness ranked using the same procedure as described in experiment 1 (with 12 repetitions). In addition, trains of single PSA pulses were included in the loudness ranking for listeners AB1 and AB3 in experiment 2. This was done because we expected the PSA pulse to be louder than the PSC pulse, and so that we could determine whether the PSA pulse dominated the loudness of the pulse-pair stimuli. The PSA pulse was also included for all listeners in experiment 3. For both experiments loudness matching was performed for IPIs of 50 and 200 μs.

3. Detection thresholds of the long-low phases

To assess the possibility that the long low phases contributed to loudness in experiment 2, we measured the detection thresholds of those long-low phases in isolation. The stimulus was a biphasic pulse with a phase duration of 344 μs and an inter-phase gap of 140 μs; it was identical to the pulse pairs in experiment 2 with IPI = 50 μs, but without the short-high phases (compare "control for audibility" with the experiment-2 stimuli in Fig. 1). We used a two-alternative forced-choice procedure, with a one-up-three-down rule. Each run consisted of two reversals with a 1-dB step size, followed by six reversals with a 0.25- dB step size. We measured the thresholds twice for each leading polarity, averaging from the last six reversals in each run, and then averaged the thresholds from the two runs.

B. Results

Figure 5 shows the mean and standard errors of the ranks obtained with the stimuli of experiment 2. As shown on the left-hand side of Fig. 5, the single anodic pulse (PSA) was ranked louder than the single cathodic pulse (PSC), consistent with the results of experiment 1a [e.g., Fig. 2(A)]. For the two listeners tested with the PSA pulse, the loudness was roughly equal to that of the maximum obtained with any of the pulse-pair stimuli. Hence, unlike in experiment 1, we cannot conclude that the cathodic pulse increased the overall loudness of any of the pulse-pair stimuli.

For the pulse pairs, loudness increased with IPI and was greater for anodic-first than for cathodic-first stimuli. This finding is similar to that observed in experiment 1a, as is the fact that the polarity effect was greater at shorter IPIs. These conclusions were supported by a rmANOVA, which revealed significant main effects of polarity [$F(1,4) = 11.56$, $p = 0.027$], IPI [$F(5,20) = 75.45$, $p < 0.001$] and an interaction between polarity and IPI [$F(5,20) = 9.14$, $p < 0.001$]. The polarity effect is further illustrated by the solid light grey bars in Fig. 4(A), which plots the difference in ranks between the two polarities at each IPI. It shows that anodic-first stimuli were ranked louder than cathodic-first stimuli, but that this was only the case for all listeners at 0, 50, and 100-μs IPI. The light grey bars in Fig. 4(B) show the results of the subsequent loudness matching at 50- and 200-μs IPI. There was a significant effect of IPI on the level difference between equally loud anodic- and cathodic-first pulses [$F(1,4) = 35.7$, $p = 0.0039$]. This reflects the fact that anodic-first stimuli were louder than cathodic-first stimuli by 0.45 and 0.09 dB at 50- and 200-μs IPI, respectively.

Figure 6 shows the mean ranks for all listeners when using symmetric-biphasic pulses and single PSA and PSC

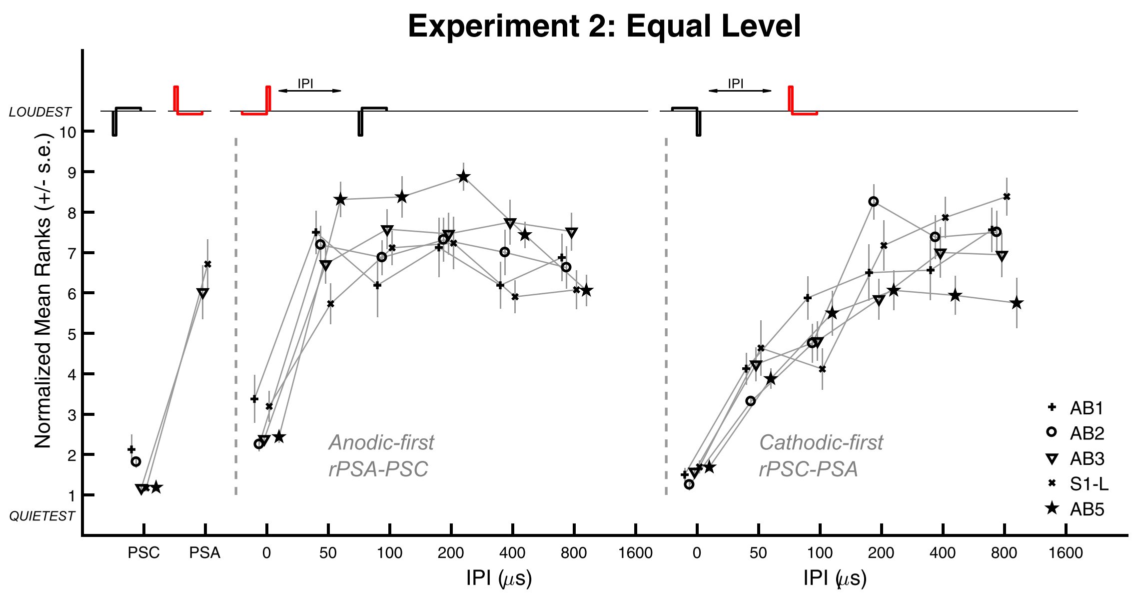

FIG. 5. (Color online) Results of the loudness ranking procedure for experiment 2 (equal level between anodic and cathodic stimulation). Mean loudness ranks for each subject are scaled between 1 and 10. As expected from previous studies with human CI listeners, PSA is louder than PSC at equal level. When combined, the pulse-pair stimuli are similar in loudness to PSA in isolation.

pulses in the loudness-ranking procedure. For the single asymmetric pulses, shown on the left of Fig. 6, PSA pulses were unsurprisingly ranked louder than PSC pulses. The symmetric biphasic pulses had either the anodic (SYM-A) or cathodic (SYM-C) phase leading. Unlike the results of experiments 1 and 2, SYM-A and SYM-C were ranked similarly for IPIs between 50 and 100–200-μs, while SYM-C was ranked *louder* than SYM-A at 400- and 800-μs IPIs. At an IPI of 0 μs the ranks were very slightly and consistently higher for the anodic-first stimuli, as in experiments 1 and 2. A rmANOVA performed on the loudness ranks given to the biphasic pulses (without PSA and PSC) showed a significant main effect of IPI [$F(5,20) = 48.88$, $p < 0.001$] and an interaction between polarity and IPI [$F(5,20) = 3.50$, $p = 0.020$], but no main effect of polarity [$F(1,4) = 6.81$, $p = 0.059$]. The polarity effect is further illustrated by the hashed light grey bars in Fig. 4(A).

Similar results were obtained in the loudness matching results [Fig. 4(B), hashed light grey bars], which show a significant effect of IPI [$F(1,4) = 74.7$, $p < 0.001$]. There was no significant difference between anodic- and cathodic-first pulses at the 50-us IPI, and cathodic-first pulses were significantly (0.26 dB) *louder* than the anodic-first pulses at the 200-μs IPI.

Figure 7 shows the current levels of the long-low phases for the stimuli used in experiment 2 (with a 50-μs IPI), relative to their detection thresholds in isolation (i.e., without the central, short-high phases). It can be seen that at their

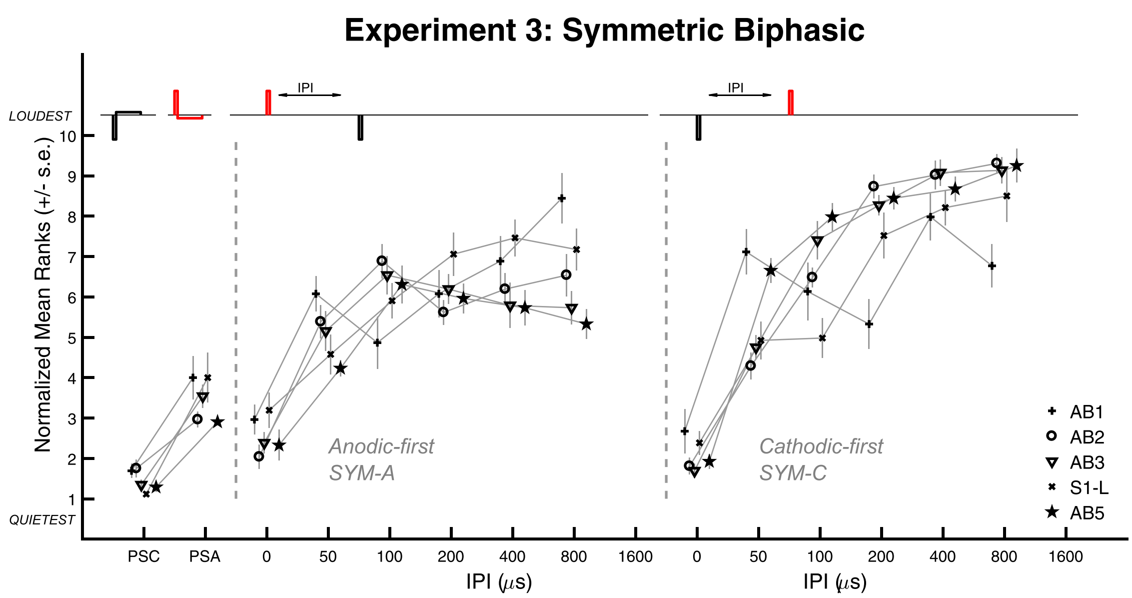

FIG. 6. (Color online) Results of the loudness ranking procedure for experiment 3 (symmetric biphasic pulses). Mean loudness ranks for each subject are scaled between 1 and 10.

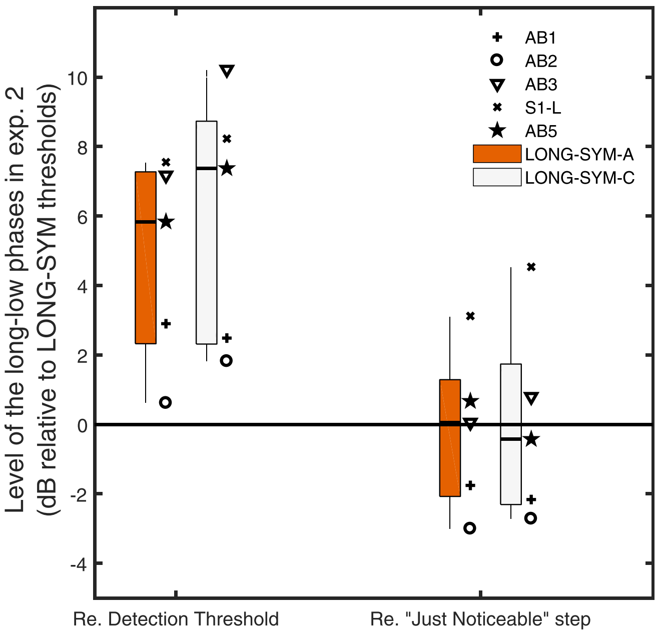

FIG. 7. (Color online) (Left) Levels of the long-low phases used in experiment 2, relative to their absolute thresholds in isolation (i.e., without the two central short-high phases). Filled boxes show the results for the first phase of the long-low phases being anodic, corresponding to the rPSC-PSA stimulus without the short-high phases. Empty boxes show the results for cathodic-leading long-low phases. (Right) Same levels, relative to the just noticeable percept of the long-low phases in isolation, obtained with a loudness-scaling chart (step 1 out of 11).

level in experiment 2, the long-low phases were above their detection thresholds in isolation for all listeners (left-hand pair of bars in Fig. 7, 5.4 dB when averaged across polarities). This was however only equivalent to step 1 ("just noticeable") on the loudness scaling chart, as shown by the right-hand pair of bars.

C. Across-experiment comparisons

Experiments 2 and 3 differed only by the presence of the long-low phases, which, based on the data shown in Fig. 7, should not contribute substantially to the overall loudness. Their presence/absence might, however, interact with the effect of IPI. To determine if this was the case, we analysed the statistical effect of changing the experiment (2 vs 3) on the loudness ranking and matching results.

A rmANOVA on the ranking results across those two experiments (excluding single pulses) showed an effect of experiment [$F(1,4) = 285$, $p < 0.001$]. This reflects the fact that the paired pulses had overall higher ranks than the single PSA in experiment 3, but not in experiment 2 (cf. Figs. 4 and 5). More importantly there was an interaction between polarity and experiment [$F(1,4) = 9.34$, $p = 0.0378$], consistent with anodic-first stimuli being overall louder than cathodic-first stimuli in experiment 2, but quieter in experiment 3. Although there was a trend for anodic-first stimuli to be louder at short IPIs in experiment 2, and quieter at long IPIs in experiment 3, there was no interaction between IPI, experiment, and polarity [$F(5,20) = 2.12$, $p = 0.11$].

There was, however, a significant effect of experiment for the loudness matching results across experiments 2 and 3 [Fig. 4(B), $F(1,4) = 19.62$, $p = 0.01$]. This reflects the fact that the loudness difference between both leading polarities changed across the two experiments, consistent with the interaction between experiment and polarity in the loudness-ranking results. Finally, there was no interaction in the loudness matching results between IPI and experiment [$F(1, 4) = 0.05$, $p = 0.83$].

IV. DISCUSSION

All experiments reported here showed significant effects of IPI on loudness. Furthermore, in all experiments, the order of the anodic and cathodic pulses within each pair significantly influenced the loudness. These order effects were similar across two different tasks, loudness ranking and loudness balancing [Fig. 4(A) vs Fig. 4(B)]. They occurred at short intervals (below 200 μs) in experiments 1a, 1b, and 2, where anodic-first stimuli were the loudest. In experiment 3, however, there were only order effects at the longest intervals and in the opposite direction (cathodic-first louder).

The number of participants tested here was low (5/6). Several factors however support the robustness of our findings. First, the use of a linear mixed-effects (LME) modeling approach (Kuznetsova *et al.*, 2015; Kuznetsova *et al.*, 2017) yielded similar results to those obtained with rmANOVA (Table III). Furthermore, the main findings obtained with the pulse-pair stimuli were consistent across two psychophysical methods, loudness matching and loudness ranking. Finally, the variability was low across listeners as well as within listeners and across conditions (e.g., Fig. 4).

A. Order effects at short IPIs (below 200 μs)

The intervals of between 0 and 200 μs where order effects occurred in experiments 1 and 2 fall well within the 7-ms central integration window proposed by McKay and McDermott (1998). Hence, although central mechanisms may influence the effect of IPI over longer time ranges, the greatest insight into the findings for IPIs up to 200 μs can be achieved by considering the different possible types of peripheral interactions. These could be interactions between APs generated by each pulse or interactions at the neuronal membrane before any generation of an AP.

In the equal-loudness experiment (1a), the pulse-pair stimuli were louder than the single-pulse stimuli at all non-zero intervals, indicating that both pulses must contribute to the overall loudness. Anodic-first pulse pairs were consistently ranked louder than cathodic-first pairs for intervals below 400 μs [Fig. 4(A)]. This order effect was small (0.4 dB at 50 μs) and decreased for larger intervals [Fig. 4(B)] but was significant and consistent across the listeners tested here.

The polarity order effect increased significantly when a within-pulse gap of 600 μs was added between the long-low and short-high phases in experiment 1b [Fig. 4(B)]. This suggests that the polarity order effect was not due to an interaction between long-low and short-high phases, as increasing the within-pulse inter-phase gap would be expected to reduce any such interactions. In experiment 2, there was an order effect similar in magnitude to that in experiment 1a,

TABLE III. Comparison of the statistical outcomes from the repeated-measures ANOVAs (as used throughout the manuscript) to a mixed-effects linear modeling (LME) approach. For the LME, the model reduction was achieved as described in Kuznetsova *et al.* (2017), with the "step" function. Significant results ($p < 0.05$) are highlighted in bold. An asterisk marks cases where the outcomes differed between the two methods. All matched levels were in dB relative to 1 μA.

Section	Dependent variable	Fixed effects	RMANOVA	LME
II B 1	Matched levels, single pulses, experiment 1a	Polarity	**$F(1,5) = 49.9$, $p < 0.001$**	**$F(1,5) = 49.9$, $p < 0.001$**
		Reversing	**$F(1,5) = 10.81$, $p = 0.022$**	**$F(1,11) = 7.64$, $p = 0.018$**
		Polarity × reversing	$F(1,5) = 1.58$, $p = 0.265$	$F(1,5) = 1.9433$, $p = 0.194$
II B 1	Matched levels, single pulses, experiment 1b	Polarity	**$F(1,4) = 33.0$, $p < 0.001$**	**$F(1,4) = 39.15$, $p = 0.0033$**
		Reversing	$F(1,4) = 3.22$, $p = 0.147$	**$F(1,8) = 7.3$, $p = 0.027$**(*)
		Polarity × reversing	**$F(1,4) = 18.4$, $p = 0.013$**	**$F(1,8) = 6.97$, $p = 0.0297$**
II B 1	Matched levels, single pulses, experiments 1a and 1b	Experiment	$F(1,4) = 3.23$, $p = 0.147$	$F(1,4) = 3.23$, $p = 0.147$
		Polarity	**$F(1,4) = 36.2$, $p = 0.00384$**	**$F(1,4) = 36.2$, $p = 0.00384$**
		Reversing	$F(1,4) = 0.007$, $p = 0.937$	$F(1,20) = 0.001$, $p = 0.975$
		Exp. × polarity	$F(1,4) = 3.29$, $p = 0.144$	$F(1,20) = 3.53$, $p = 0.075$
		Experiment × reversing	$F(1,4) = 6.09$, $p = 0.069$	$F(1,20) = 2.99$, $p = 0.0993$
		Polarity × reversing	**$F(1,4) = 20.8$, $p = 0.0103$**	**$F(1,20) = 38.04$, $p < 0.001$**
		Experiment × polarity × reversing	**$F(1,4) = 13.5$, $p = 0.0213$**	**$F(1,20) = 19.8$, $p < 0.001$**
II B 2	Loudness ranks, paired pulses, experiment 1a	Polarity	**$F(1,5) = 131.1$, $p < 0.001$**	**$F(1,30) = 264$, $p < 0.001$**
		IPI	**$F(5,25) = 113.8$, $p < 0.001$**	**$F(5,30) = 123$, $p < 0.001$**
		Polarity × IPI	**$F(5,25) = 34.72$, $p < 0.001$**	**$F(5,30) = 27.7$, $p < 0.001$**
II B 2	Matched levels, paired pulses, experiment 1a	Polarity	**$F(1,4) = 101.8$, $p < 0.001$**	**$F(1,14) = 18.1$, $p < 0.001$**
		IPI	$F(1,4) = 3.01$, $p = 0.16$	$F(1,13) = 3.33$, $p = 0.091$
		Polarity × IPI	$F(1,4) = 3.01$, $p = 0.16$	$F(1,12) = 4.13$, $p = 0.065$
II B 3	Matched levels, paired pulses, experiment 1a and 1b	Experiment	$F(1,4) = 1.93$, $p = 0.237$	$F(1,4) = 1.93$, $p = 0.237$
		Polarity	**$F(1,4) = 183$, $p < 0.001$**	**$F(1,26) = 147$, $p < 0.001$**
		IPI	**$F(1,4) = 10.1$, $p = 0.0337$**	**$F(1,26) = 17.2$, $p < 0.001$**
		Experiment × polarity	**$F(1,4) = 16.4$, $p = 0.0154$**	**$F(1,26) = 17.4$, $p < 0.001$**
		Experiment × IPI	$F(1,4) = 2.30$, $p = 0.204$	$F(1,25) = 0.995$, $p = 0.328$
		polarity × IPI	**$F(1,4) = 12.8$, $p = 0.0233$**	**$F(1,26) = 18.7$, $p < 0.001$**
		Experiment × polarity × IPI	$F(1,4) = 3.19$, $p = 0.149$	$F(1,24) = 1.41$, $p = 0.246$
III B	Loudness ranks, paired pulses, experiment 2	Polarity	**$F(1,4) = 11.56$, $p = 0.027$**	**$F(1,48) = 33.3$, $p < 0.001$**
		IPI	**$F(5,20) = 75.45$, $p < 0.001$**	**$F(5,48) = 65.9$, $p < 0.001$**
		Polarity × IPI	**$F(5,20) = 9.14$, $p < 0.001$**	**$F(5,48) = 8.64$, p < 0.001**
III B	Matched levels, paired pulses, experiment 2	Polarity	**$F(1,4) = 50.3$, $p = 0.002$**	**$F(1,12) = 33.1$, $p < 0.001$**
		IPI	**$F(1,4) = 14.84$, $p = 0.0183$**	**$F(1,12) = 28.5$, $p < 0.001$**
		Polarity × IPI	**$F(1,4) = 35.7$, $p = 0.00395$**	**$F(1,12) = 15.1$, $p = 0.0022$**
III B	Loudness ranks, paired pulses, experiment 3	Polarity	$F(1,4) = 6.81$, $p = 0.059$	**$F(1,48) = 18.33$, $p < 0.001$**(*)
		IPI	**$F(5,20) = 48.9$. $p < 0.001$**	**$F(5,48) = 46.9$, $p < 0.001$**
		Polarity × IPI	**$F(5,20) = 3.50$, $p = 0.020$**	**$F(5,48) = 3.14$, $p = 0.0158$**
III B	Matched levels, paired pulses, experiment 3	Polarity	$F(1,4) = 2.15$, $p = 0.217$	$F(1,4) = 2.15$, $p = 0.217$
		IPI	**$F(1,4) = 74.7$, $p < 0.001$**	**$F(1,8) = 74.7$, $p < 0.001$**
		Polarity × IPI	**$F(1,4) = 74.7$, $p < 0.001$**	**$F(1,8) = 74.7$, $p < 0.001$**
III C	Loudness ranks, paired pulses, experiments 2 and 3	Experiment	**$F(1,4) = 285$, $p < 0.001$**	$F(1,106) = 1.69$, $p = 0.197$(*)
		Experiment × polarity	**$F(1,4) = 9.34$, $p = 0.0378$**	**$F(1,106) = 103$, $p < 0.001$**
		Experiment × polarity × IPI	$F(5,20) = 2.12$, $p = 0.11$	$F(5,96) = 1.777$, $p = 0.1247$
III C	Matched levels, paired pulses, experiments 2 and 3	Experiment	$F(1,4) = 0.056$, $p = 0.824$	$F(1,4) = 0.056$, $p = 0.824$
		Experiment × polarity	**$F(1,4) = 19{,}62$, $p = 0.0114$**	**$F(1,26) = 35.4$, $p < 0.001$**
		Experiment × polarity × IPI	$F(1,4) = 0.0527$, $p = 0.830$	$F(1,24) = 0.0143$, $p = 0.9057$

even though the two pulses had the same level. Order effects disappeared at short IPIs when the long-low phases were removed completely (experiment 3).

In the following, we discuss two phenomena that, in principle, could result in order effects at short IPIs: spike collision and charge summation at the level of the neuronal membrane.

1. Spike collision hypothesis

Anodic stimulation likely generates APs more centrally than cathodic stimulation (Macherey *et al.*, 2017; Miller *et al.*, 1999; Ranck, 1975; Rattay *et al.*, 2001; Undurraga *et al.*, 2013). If cathodic stimulation were to create an AP at a peripheral node of Ranvier in the SGNs, the AP would have to travel across the soma. The soma has a higher capacitance than the peripheral and central nodes (Adamo and Daigneault, 1973; Liberman and Oliver, 1984; Robertson, 1976), hence, a relatively long time constant of depolarization. This has been suggested as the mechanism for the difference in latency between peripheral and central processes (e.g., Javel and Shepherd, 2000). Assuming that loudness is related to the number of spikes transmitted from the SGN to the brain, the lower loudness for cathodic-first stimuli in experiments 1 and 2 is therefore consistent with a "collision" hypothesis: APs created at the periphery by the cathodic pulse travel across the soma and get blocked (or block) the APs created more centrally by the anodic pulse. Conversely, for anodic-first stimuli, APs generated by the anodic pulse would propagate centrally, before the APs generated by the cathodic pulse (at the peripheral processes) could catch up. This would increase the chance of APs elicited by both pulses reaching the brain.

If the order effects presented here are due to a latency difference between spikes elicited by anodic and cathodic stimulation, then this difference (largest at 50–100 μs) falls within the lowest range of that observed in animal recordings, which is typically 200 μs or more, albeit with a large variability (Fig. 5 in Miller *et al.*, 1999). Even though 50–100 μs is below the average absolute refractory period of 400 μs (Boulet *et al.*, 2016), a small number of neurons might have the ability to fire twice with such short IPIs (Miller *et al.*, 2001a).

One phenomenon that the spike collision hypothesis does not take into account is the propagation of spikes from central to peripheral processes, also called antidromic propagation. The hypothesis predicts that antidromic propagation would reduce the size of the effects observed here because the anodic pulse, which excites the central axon, would block the spikes initiated at the peripheral process by the cathodic pulse, and this blocking would be greatest when the anodic stimulus is presented first. Additionally, if the effects of antidromic propagation had a different time course than the main effect, this would disrupt our estimate of the temporal dynamics. This cannot be ruled out, although it is worth noting evidence that antidromic propagation is not stable, particularly when it comes to traveling across the soma (Brown, 1994). Finally, antidromic propagation has only been shown in animal studies with healthy peripheral axons (e.g., Miller *et al.*, 2004), which is likely not the case in many human CI listeners.

2. Charge summation at the membrane

The neuronal membrane behaves approximately as a leaky integrator (Lapicque, 1907) and, for SGNs, the time constant of this integrator is estimated to be around or above 100 μs (de Balthasar *et al.*, 2003; Cosentino *et al.*, 2015; Kwon and van den Honert, 2009; Macherey *et al.*, 2007; Middlebrooks, 2004). This is longer than the duration of the short-high phases used here. Hence, at short IPIs, the absolute peak value of the transmembrane potential will be larger for the first pulse than the second pulse. In other words, the first pulse will partially cancel the second pulse. The opposite interaction can also occur, whereby the second pulse reduces the duration over which the membrane remains polarized after the first pulse, thereby reducing the probability of an AP being elicited by the first pulse (e.g., van den Honert and Mortimer, 1979).

More complex charge summations might stem from the multiplicity of nodes of Ranvier on the SGNs and their interconnection (Joucla and Yvert, 2012; Rattay *et al.*, 2001). For example, peripheral and central nodes might exhibit different time constants of charge integration (Cartee *et al.*, 2006), which could affect how the two pulses cancel each other in our paradigm. Furthermore, hyperpolarization at central nodes by cathodic currents can create a so-called cathodal block, which prevents a peripherally generated AP from propagating to the cochlear nucleus (Frijns *et al.*, 1996; Macherey *et al.*, 2017). The order of presentation of anodic and cathodic pulses could affect the presence of such block, and, more generally, affect the integration of charge across the various nodes of Ranvier (Rattay *et al.*, 2001).

B. Effects at longer intervals (above 400 μs)

At longer intervals (above 300–400 μs), there were no polarity order effects in experiments 1a and 2, but cathodic-first stimuli were louder than anodic-first stimuli in experiment 3 [Fig. 4(A)]. At those interval durations, the underlying mechanisms are likely to be driven by refractoriness and/or central integration rather than charge cancellation at the level of the neuronal membrane (Cosentino *et al.*, 2015; McKay and McDermott, 1998). In other words, there is a higher chance for both pulses to elicit a neural response on their own, rather than being integrated at the level of the neuronal membrane.

In both experiments 2 and 3, the individual pulses were presented at the same current level, with the consequence that the anodic pulse in each pair would have dominated the loudness to some extent. Forward masking of a pulse by a single-pulse masker is strong for inter-pulse durations between 400 and 800 μs, and has been attributed to refractoriness (e.g., Nelson and Donaldson, 2001). We would expect such refractory effects to be greater when the first pulse (masker) is more effective than the second pulse (probe) than vice versa. Similarly, because the anodic phase of SYM pulses elicits a much stronger neural response than the cathodic phase (Hughes *et al.*, 2017; Undurraga *et al.*, 2010), then, following anodic stimulation, a large proportion of the neurons will be under a state of refractoriness, thereby reducing the response to the cathodic phase. This is consistent with anodic-first stimuli being ranked quieter [Fig. 4(A)] than cathodic-first stimuli (where both pulses are likely to elicit a neural response) for IPIs of 400–800 μs. These refractory effects could occur either in the AN or more centrally. In experiments 1a and 2, the ratio of contribution from each pulse might have been closer to unity, explaining why there were no order effects at the longest intervals in those experiments. This would have been true in experiment 1 because the two pulses in each pair were loudness balanced prior to the main experiment. In experiment 2 the long opposite-polarity phases of each pulse may have contributed slightly to their loudness (cf. Fig. 7), reducing the difference in loudness between (R)PSA and (R)PSC pulses. It is also possible that the dominance of the anodic phase in the SYM pulses of experiment 3 is responsible for the absence of an effect of polarity at IPIs of between 50 and 200 μs in that experiment. However, the mechanisms by which that might occur are less clear than the refractoriness effects that, we suggest, are responsible for the greater loudness of SYM-C than SYM-A stimuli at long intervals.

V. CONCLUSION

At very short IPIs (below $100\,\mu$s) and when equating loudness by means of asymmetric pulses, anodic-first stimulation is louder than cathodic-first stimulation. This effect is in agreement with (but does not prove) a hypothesis based on a difference in latency between anodic and cathodic stimulation. Alternative explanations such as charge cancellation or cathodal blocking cannot, however, be excluded, as they would all affect the loudness judgements in the same direction. A similar result was obtained using asymmetric pulses of equal level, rather than equal loudness.

For symmetric biphasic pulses, and at longer IPIs, the anodic-first stimulus was quieter than the cathodic-first stimulus. This is consistent with the idea that, at these longer IPIs, the polarity order effects are due to refractoriness, which has a greater effect when the stronger (anodic) response occurs first. Such refractory effects could occur either at the level of the AN or more centrally.

ACKNOWLEDGMENTS

This research was supported by Award No. RG91365 from the Medical Research Council to R.P.C., and by a grant from the Oticon Centre of Excellence for Hearing and Speech Sciences (CHeSS) to F.G. The authors would like to thank the listeners for participating in the several sessions of this study and Suyash N. Joshi for helpful discussions.

[1]The distribution of ranks across trials deviated in some occasions from normality, particularly for stimuli ranked at the loudest or quietest end of the range. Visual inspection of quantile-quantile plots revealed that these deviations were overall rare. Accordingly, running the statistical analysis with the median ranks instead of the mean ranks did not change the main conclusions.

Adamo, N. J., and Daigneault, E. A. (**1973**). "Ultrastructural features of neurons and nerve fibres in the spiral ganglia of cats," J. Neurocytol. **2**, 91–103.

Bahmer, A., Adel, Y., and Baumann, U. (**2017**). "Preventing facial nerve stimulation by triphasic pulse stimulation in cochlear implant users: Intraoperative recordings," Otol. Neurotol. **38**, e438–e444.

Bahmer, A., and Baumann, U. (**2013**). "Effects of electrical pulse polarity shape on intra cochlear neural responses in humans: Triphasic pulses with cathodic second phase," Hear. Res. **306**, 123–130.

Bahmer, A., and Baumann, U. (**2016**). "The underlying mechanism of preventing facial nerve stimulation by triphasic pulse stimulation in cochlear implant users assessed with objective measure," Otol. Neurotol. **37**, 1231–1237.

Bahmer, A., Polak, M., and Baumann, U. (**2010**). "Recording of electrically evoked auditory brainstem responses after electrical stimulation with biphasic, triphasic and precision triphasic pulses," Hear. Res. **259**, 75–85.

Boulet, J., White, M., and Bruce, I. C. (**2016**). "Temporal considerations for stimulating spiral ganglion neurons with cochlear implants," J. Assoc. Res. Otolaryngol. **17**, 1–17.

Brown, M. C. (**1994**). "Antidromic responses of single units from the spiral ganglion," J. Neurophysiol. **71**, 1835–1847.

Brummer, S. B., and Turner, M. J. (**1977**). "Electrochemical considerations for safe electrical stimulation of the nervous system with platinum electrodes," IEEE Trans. Biomed. Eng. **BME-24**, 59–63.

Carlyon, R. P., Cosentino, S., Deeks, J. M., Parkinson, W., and Arenberg, J. A. (**2018**). "Effect of stimulus polarity on detection thresholds in cochlear implant users: Relationships with average threshold, gap detection, and rate discrimination," J. Assoc. Res. Otolaryngol. 1–9.

Carlyon, R. P., Deeks, J. M., and Macherey, O. (**2013**). "Polarity effects on place pitch and loudness for three cochlear-implant designs and at different cochlear sites," J. Acoust. Soc. Am. **134**, 503–509.

Cartee, L. A., Miller, C. A., and van den Honert, C. (**2006**). "Spiral ganglion cell site of excitation I: Comparison of scala tympani and intrameatal electrode responses," Hear. Res. **215**, 10–21.

Cosentino, S., Deeks, J. M., and Carlyon, R. P. (**2015**). "Procedural factors that affect psychophysical measures of spatial selectivity in cochlear implant users," Trends Hear. **19**, 1–16.

de Balthasar, C., Boëx, C., Cosendai, G., Valentini, G., Sigrist, A., and Pelizzone, M. (**2003**). "Channel interactions with high-rate biphasic electrical stimulation in cochlear implant subjects," Hear. Res. **182**, 77–87.

Frijns, J. H. M., De Snoo, S. L., and Ten Kate, J. H. (**1996**). "Spatial selectivity in a rotationally symmetric model of the electrically stimulated cochlea," Hear. Res. **95**, 33–48.

Hughes, M. L., Goehring, J. L., and Baudhuin, J. L. (**2017**). "Effects of stimulus polarity and artifact reduction method on the electrically evoked compound action potential," Ear Hear. **38**, 332–343.

Javel, E., and Shepherd, R. K. (**2000**). "Electrical stimulation of the auditory nerve. III. Response initiation sites and temporal fine structure," Hear. Res. **140**, 45–76.

Johnsson, L.-G., Hawkins, J. E., and Kingsley, T. C. (**1981**). "Aminoglycoside-induced cochlear pathology in man," Acta Otolaryngol. Suppl. **383**, 1–19.

Joucla, S., and Yvert, B. (**2012**). "Modeling extracellular electrical neural stimulation: From basic understanding to MEA-based applications," J. Physiol. Paris **106**, 146–158.

Karg, S. A., Lackner, C., and Hemmert, W. (**2013**). "Temporal interaction in electrical hearing elucidates auditory nerve dynamics in humans," Hear. Res. **299**, 10–18.

Kim, K. X., and Rutherford, M. A. (**2016**). "Maturation of Na_V and K_V channel topographies in the auditory nerve spike initiator before and after developmental onset of hearing function," J. Neurosci. **36**, 2111–2118.

Kuznetsova, A., Brockhoff, P. B., and Christensen, R. H. B. (**2017**). "lmerTest Package: Tests in linear mixed effects models," J. Stat. Softw. **82**, 1–26..

Kuznetsova, A., Christensen, R. H. B., Bavay, C., and Brockhoff, P. B. (**2015**). "Automated mixed ANOVA modeling of sensory and consumer data," Food Qual. Prefer. **40**, 31–38.

Kwon, B. J., and van den Honert, C. (**2009**). "Spatial and temporal effects of interleaved masking in cochlear implants," J. Assoc. Res. Otolaryngol. **10**, 447–457.

Landsberger, D. M., Svrakic, M., Roland, J. T., and Svirsky, M. (**2015**). "The relationship between insertion angles, default frequency allocations, and spiral ganglion place pitch in cochlear implants," Ear Hear. **36**, e207–e213.

Lapicque, L. (**1907**). "Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation" ("Quantitative investigations of electrical nerve excitation treated as polarization"), J. Physiol. Pathol. Générale **9**, 620–635.

Leake, P. A., and Hradek, G. T. (**1988**). "Cochlear pathology of long term neomycin induced deafness in cats," Hear. Res. **33**, 11–33.

Liberman, M. C., and Oliver, M. E. (**1984**). "Morphometry of intracellularly labeled neurons of the auditory nerve: Correlations with functional properties," J. Comp. Neurol. **223**, 163–176.

Litovsky, R. Y., Goupell, M. J., Kan, A., and Landsberger, D. M. (**2017**). "Use of research interfaces for psychophysical studies with cochlear-implant users," Trends Hear. **21**, 233121651773646.

Long, C. J., Nimmo-Smith, I., Baguley, D. M., O'Driscoll, M., Ramsden, R., Otto, S. R., Axon, P. R., and Carlyon, R. P. (**2005**). "Optimizing the clinical fit of auditory brain stem implants," Ear Hear. **26**, 251–262.

Macherey, O., Carlyon, R. P., Chatron, J., and Roman, S. (**2017**). "Effect of pulse polarity on thresholds and on non-monotonic loudness growth in cochlear implant users," J. Assoc. Res. Otolaryngol. **18**, 513–527.

Macherey, O., Carlyon, R. P., van Wieringen, A., Deeks, J. M., and Wouters, J. (**2008**). "Higher sensitivity of human auditory nerve fibers to positive electrical currents," J. Assoc. Res. Otolaryngol. **9**, 241–251.

Macherey, O., Carlyon, R. P., van Wieringen, A., and Wouters, J. (**2007**). "A dual-process integrator-resonator model of the electrically stimulated human auditory nerve," J. Assoc. Res. Otolaryngol. **8**, 84–104.

Macherey, O., van Wieringen, A., Carlyon, R. P., Deeks, J. M., and Wouters, J. (**2006**). "Asymmetric pulses in cochlear implants: Effects of pulse shape, polarity, and rate," J. Assoc. Res. Otolaryngol. **7**, 253–266.

Macherey, O., van Wieringen, A., Carlyon, R. P., Dhooge, I., and Wouters, J. (**2010**). "Forward-masking patterns produced by symmetric and asymmetric pulse shapes in electric hearing," J. Acoust. Soc. Am. **127**, 326–338.

McKay, C. M., and McDermott, H. J. (**1998**). "Loudness perception with pulsatile electrical stimulation: The effect of interpulse intervals," J. Acoust. Soc. Am. **104**, 1061–1074.

Mesnildrey, Q. (**2017**). "Towards a better understanding of the cochlear implant—Auditory nerve interface: From intracochlear electrical recordings to psychophysics," Ph.D. thesis, Aix-Marseille Université.

Middlebrooks, J. C. (**2004**). "Effects of cochlear-implant pulse rate and inter-channel timing on channel interactions and thresholds," J. Acoust. Soc. Am. **116**, 452–468.

Miller, C. A., Abbas, P. J., Hay-McCutcheon, M. J., Robinson, B. K., Nourski, K. V., and Jeng, F. C. (**2004**). "Intracochlear and extracochlear ECAPs suggest antidromic action potentials," Hear. Res. **198**, 75–86.

Miller, C. A., Abbas, P. J., and Robinson, B. K. (**2001a**). "Response properties of the refractory auditory nerve fiber," J. Assoc. Res. Otolaryngol. **2**, 216–232.

Miller, C. A., Abbas, P. J., Robinson, B. K., Rubinstein, J. T., and Matsuoka, A. J. (**1999**). "Electrically evoked single-fiber action potentials from cat: Responses to monopolar, monophasic stimulation," Hear. Res. **130**, 197–218.

Miller, C. A., Robinson, B. K., Rubinstein, J. T., Abbas, P. J., and Runge-Samuelson, C. L. (**2001b**). "Auditory nerve responses to monophasic and biphasic electric stimuli," Hear. Res. **151**, 79–94.

Nelson, D. A., and Donaldson, G. S. (**2001**). "Psychophysical recovery from single-pulse forward masking in electric hearing," J. Acoust. Soc. Am. **109**, 2921–2933.

Ranck, J. B. J. (**1975**). "Which elements are excited in electrical stimulation of mammalian central nervous system: A review," Brain Res. **98**, 417–440.

Rattay, F., Lutter, P., and Felix, H. (**2001**). "A model of the electrically excited human cochlear neuron. I. Contribution of neural substructures to the generation and propagation of spikes," Hear. Res. **153**, 43–63.

Robertson, D. (**1976**). "Possible relation between structure and spike shapes of neurones in guinea pig cochlear ganglion," Brain Res. **109**, 487–496.

Undurraga, J. A., Carlyon, R. P., Wouters, J., and van Wieringen, A. (**2013**). "The polarity sensitivity of the electrically stimulated human auditory nerve measured at the level of the brainstem," J. Assoc. Res. Otolaryngol. **14**, 359–377.

Undurraga, J. A., van Wieringen, A., Carlyon, R. P., Macherey, O., and Wouters, J. (**2010**). "Polarity effects on neural responses of the electrically stimulated auditory nerve at different cochlear sites," Hear. Res. **269**, 146–161.

van den Honert, C., and Mortimer, J. T. (**1979**). "The response of the myelinated nerve fiber to short duration biphasic stimulating currents," Ann. Biomed. Eng. **7**, 117–125.

van den Honert, C., and Stypulkowski, P. H. (**1984**). "Physiological properties of the electrically stimulated auditory nerve. II. Single fiber recordings," Hear. Res. **14**, 225–243.

van Wieringen, A., Carlyon, R. P., Laneau, J., and Wouters, J. (**2005**). "Effects of waveform shape on human sensitivity to electrical stimulation of the inner ear," Hear. Res. **200**, 73–86.